Immunotherapy in combination with neoadjuvant anthracycline-free chemotherapy for triple-negative early breast cancer: A case report

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Received February 18, 2023; Accepted June 1, 2023

DOI: 10.3892/ol.2023.13961

Abstract. Immunotherapy is a promising anticancer strategy. In the present report, the case of a 36-year-old female patient with pathologically diagnosed, left triple-negative breast cancer and axillary lymph node involvement is reported. The patient received immunotherapy in combination with neoadjuvant anthracycline-free chemotherapy for six cycles, before undergoing left mastectomy and left axillary lymph node dissection. The postoperative pathology was a complete response to treatment, involving eradication of tumor from both the breast and the relevant lymph nodes. However, thyroid dysfunction occurred after two cycles of neoadjuvant treatment. The clinical presentation of the thyroid disorder was transient hyperthyroidism for 4 weeks and subsequent hypothyroidism, which required hormone replacement therapy.

Introduction

Immunotherapy is a new promising anticancer strategy. Immune checkpoint inhibitors (ICPIs) block certain immune inhibitory 'checkpoints', such as programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1) or cytotoxic T-lymphocyte antigen 4, preventing these inhibitors from blocking T-cell proliferation and activation against tumor cells (1). In patients with early-stage, triple-negative breast cancer, neoadjuvant treatment with chemotherapy in combination with ICPIs improves pathological complete response (pCR) rates (2,3). Among patients with metastatic triple-negative breast cancer with positive PD-L1 status, chemotherapy in combination with ICPIs has demonstrated a notable and clinically meaningful improvement in progression-free survival (4,5). Despite the clinical benefit of ICPI treatment, ICPI use is associated with a spectrum of adverse effects involving any organ, most commonly those of the gastrointestinal tract, endocrine glands, skin and liver (6,7). Thyroid dysfunction is one of the most frequent endocrine adverse events associated with ICPIs and is present in 3-15% of patients treated with either anti-PD-1 or anti-PD-L1 (2-5).

In the present study, the case of a 36-year-old female patient pathologically diagnosed with left, triple-negative breast cancer and left axillary lymph node metastasis is reported. Prior to surgery, this patient received neoadjuvant anthracycline-free chemotherapy and anti-PD-1 treatment for six cycles. The postoperative pathology showed a pCR for both the breast and the axillary lymph node. Despite the meaningful clinical improvement, the patient suffered from transient hyperthyroidism for 4 weeks and subsequent hypothyroidism requiring sustained hormone replacement.

Case report

In June 2020, a 36-year-old female patient attended The Outpatient Department of The Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) due to a lump present in the left breast for half a year. Physical examination revealed a hard and poorly mobile mass in the outer upper quadrant of the left breast. An ultrasound displayed an irregular hypoechoic mass of 21.4x14.5 mm in the 2 o'clock orientation of the left breast with several abnormal axillary lymph nodes (Fig. 1). Magnetic resonance imaging (MRI) of the breast revealed an irregularly-shaped and lobulated mass in the outer upper quadrant of the left breast with enlarged axillary lymph nodes. Any distant metastases were not detected by radiological examinations, including brain, chest and upper abdominal computed tomography and bone scintigraphy.

In addition, a core needle biopsy confirmed left breast-invasive ductal carcinoma and left axillary lymph node metastasis (Fig. 2). Immunohistochemistry of paraffin-embedded breast tissues was negative for both hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2). For

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Key words: immunotherapy, neoadjuvant, early breast cancer, thyroid dysfunction, case report

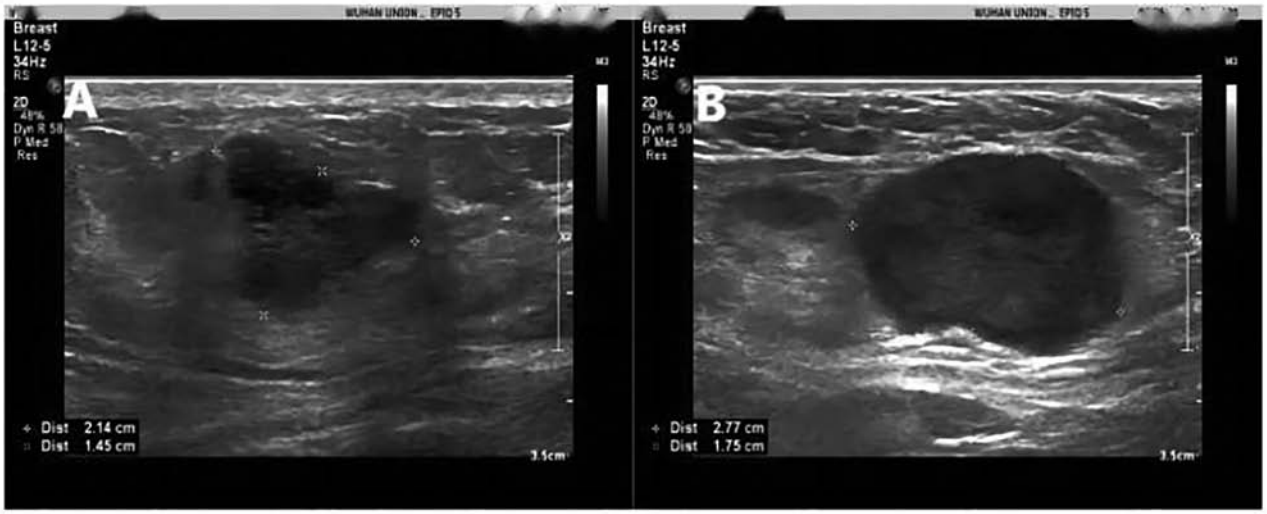

Figure 1. Ultrasound images of the left breast and axillary lymph nodes. (A) A 21.4x14.5-mm, irregularly-shaped and hypoechoic mass was visible in the 2 o'clock orientation of the left breast. (B) Several abnormal lymph nodes were present in the left axillary.

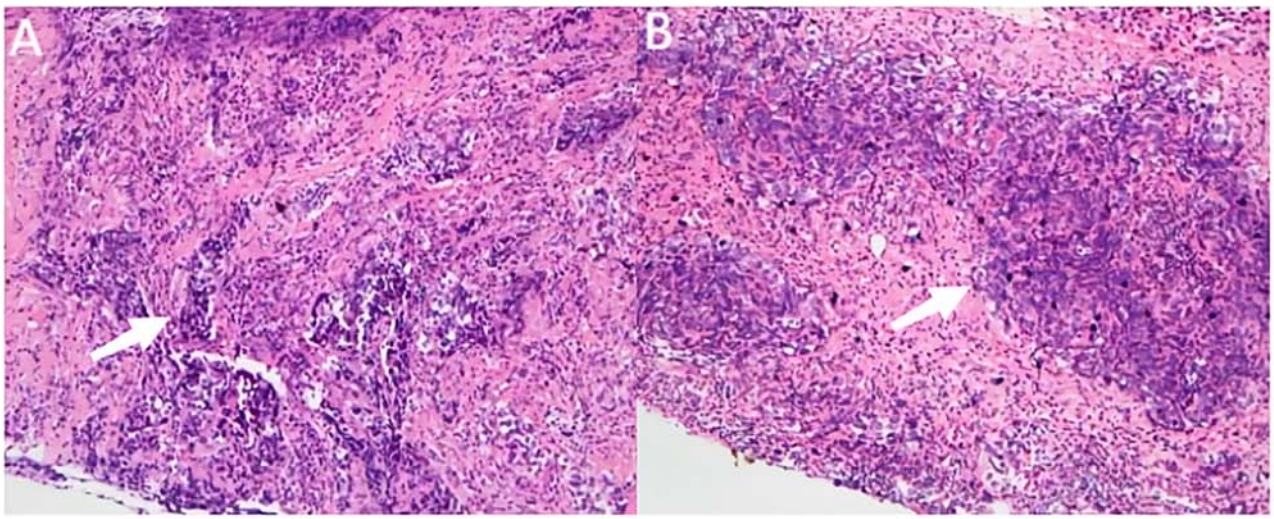

Figure 2. Pathological results (H&E staining; magnification, x100) of the core needle biopsies. (A) The left breast mass was diagnosed as invasive ductal carcinoma. (B) The left axillary lymph node was confirmed as a carcinoma metastasis. Arrows indicate carcinoma.

immunohistochemistry, the breast samples of core needle biopsy were fixed in 10% formalin at room temperature for 24 h. The sections (3-μm thick) of paraffin-embedded breast cancer samples were heated at 58˚C for 2 h and then deparaffinized in xylene for 10 min and hydrated in a series of graded alcohols (100% ethanol for 2 min, 95% ethanol for 2 min, 80% ethanol for 2 min, 70% ethanol for 2 min). After blocking with working fluid (cat. no. DM841; Dako; Agilent Technologies, Inc.) at room temperature for 3 min, the samples were immersed in citrate buffer (0.01M, pH 9.0) and heated at 121˚C in a microwave oven for 10 min. To block endogenous peroxidase activity, samples were incubated with 3% hydrogen peroxide at 20˚C for 30 min. Subsequently, the samples were probed with primary antibodies against estrogen receptor (working fluid; cat. no. SP1; Roche Diagnostics Co., Ltd.), progesterone receptor (working fluid; cat. no. 1E2; Roche Diagnostics Co., Ltd.) or HER2 (working fluid; cat. no. 4B5; Roche Diagnostics Co., Ltd.) at 37˚C for 32 min. The samples

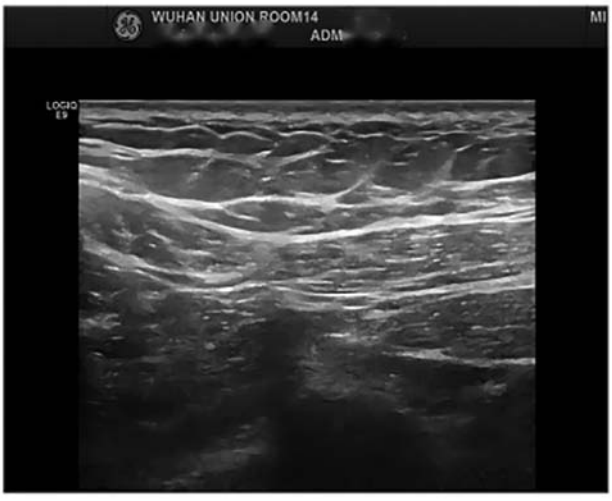

Figure 3. Ultrasound images of the left breast. Complete response of the left breast after six cycles of neoadjuvant therapy.

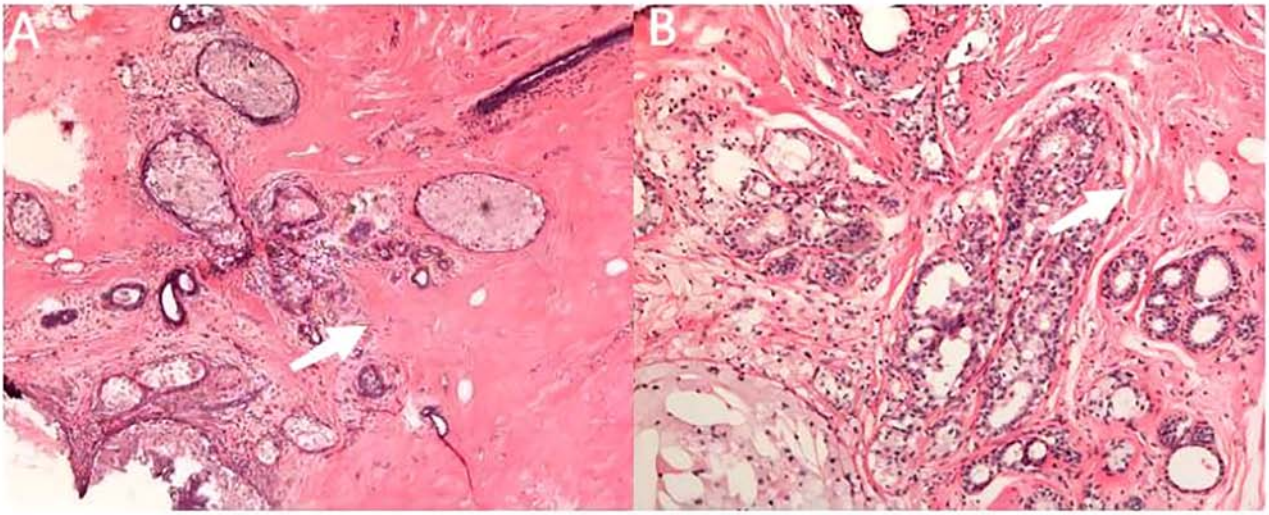

Figure 4. Pathological complete response of the breast and stromal hyaline degeneration after six cycles of neoadjuvant therapy. H&E staining at (A) x40 magnification and (B) x100 magnification. Arrows indicate stromal hyaline degeneration.

were then incubated with a biotinylated anti-mouse/rabbit secondary antibody (1:500 dilution; cat. no. D0486; Dako; Agilent Technologies, Inc.) at 37˚C for 15 min. The ultraview DAB IHC detection kit (version 1.7; Roche Diagnostics Co., Ltd.) was used visualize the bands. The sections were counterstained with haematoxylin and mounted. The sections were visualized using a light microscope (Olympus BX53; Olympus Corp.) at x100 magnification.

Following the National Comprehensive Cancer Network breast cancer guidelines (8), neoadjuvant therapy was suggested for treatment after discussions with the patient. The patient received 260 mg/m^2 of nab-paclitaxel every 2 weeks with anti-PD-1 antibody, 200 mg of camrelizumab, every 2 weeks for the first two cycles. Clinical CR, partial response (PR) and stable disease (SD) were evaluated with reference to the definitions of the Response Evaluation Criteria in Advanced Solid Tumors version 1.1 (9). Before the third cycle of therapy, the breast ultrasound showed clinical SD; thus, the patient received additional platinum therapy consisting of 50 mg lobaplatin every 2 weeks for the next two cycles. Before the fifth cycle, the breast ultrasound indicated clinical CR, but the MRI showed clinical PR. Therefore, the decision was made to continue with an additional two cycles of the prior therapy regimen after communicating with the patient. The last preoperative evaluation occurred after completing six cycles of neoadjuvant therapy in total, and the breast ultrasound (Fig. 3) and the MRI showed clinical CR and PR, respectively. Subsequently, both the clinicians and the patient decided to pursue surgical treatment. After surgery, both the left breast and axillary lymph nodes achieved pCR based on analyzing the specimens of the modified radical mastectomy (Fig. 4).

Although the patient exhibited a good therapeutic response, the patient did suffer from asymptomatic thyroid dysfunction by empirical testing for thyroid stimulating hormone (TSH). Hypothyroidism was preceded by transient hyperthyroidism. The first TSH levels were 0.2732 mIU/l (normal reference range, 0.35-4.94 mIU/l) after two cycles of neoadjuvant therapy. The second TSH levels were 0.0171 mIU/l after four cycles of neoadjuvant therapy without any additional interventions. The third TSH levels were 96.2476 mIU/l after six cycles of neoadjuvant therapy; thus, the hypothyroidism was classified as G2 according to the Common Terminology Criteria for Adverse Events grading system (6). Hormone replacement therapy with levothyroxine and the monitoring of TSH and free thyroxine (FT4) levels are currently ongoing. The first visit was 3 months after radical surgery, which was performed in October 2020 and the latest visit was 2 years after surgery. The CR status has been maintained for >2 years.

Discussion

Monotherapy with the anti-PD-1 antibody pembrolizumab has demonstrated durable antitumor activity for previously-treated metastatic, triple-negative breast cancer (10). Treatment with pembrolizumab plus chemotherapy has also achieved a notable and clinically meaningful improvement in progression-free survival among patients with metastatic, triple-negative breast cancer with positive PD-L1 status (5). Treatment with the anti-PD-L1 antibody atezolizumab plus nab-paclitaxel also extended progression-free survival among patients with metastatic, triple-negative breast cancer (4). Pembrolizumab plus neoadjuvant chemotherapy doubled the estimated pCR rate in female patients with early-stage HR$^+$/HER2$^-$ or triple-negative breast cancer compared with the standard neoadjuvant chemotherapy (11). In another study, the number of patients with early-stage, triple-negative breast cancer who demonstrated a pCR was markedly higher among those patients who received pembrolizumab plus neoadjuvant chemotherapy (64.8%) than among those who received placebo plus neoadjuvant chemotherapy (51.2%) (3). Neoadjuvant treatment with atezolizumab in combination with nab-paclitaxel and anthracycline-based chemotherapy has also been indicated to markedly improve the pCR rate with an acceptable safety profile, i.e., safety was consistent with the known profiles of the individual drugs, compared with placebo plus nab-paclitaxel and anthracycline-based chemotherapy (2). In the present case report, six cycles of neoadjuvant anthracycline-free chemotherapy with

camrelizumab treatment achieved a pCR. To the best of our knowledge, this is the first report of immunotherapy in combination with neoadjuvant anthracycline-free chemotherapy for triple-negative early breast cancer. It is considered a challenge to evaluate clinical CR after neoadjuvant therapy, particularly when ultrasonography and MRI show different results. Usually, ultrasonography is combined with MRI to evaluate the response of neoadjuvant therapy, as in the present case report.

Immune-related adverse events refer to inflammatory side effects induced by immune checkpoint inhibitors. Immune-related adverse events most commonly involve the gastrointestinal tract, endocrine glands, skin and liver. Immune-related events also involve the central nervous, cardiovascular, pulmonary, musculoskeletal and hematologic systems, but less frequently (7,12). Most adverse events are spontaneously relieved; however, hypothyroidism may be a permanent side effect. Hyperthyroidism is almost always resolving, followed or not by a hypothyroidism phase (1). In the present case report, persistent hypothyroidism occurred after transient hyperthyroidism lasting for four weeks.

Immune-related thyroid dysfunction is relatively common. In total, 7-15% of the population suffered from hypothyroidism and 3-6% of the population suffered from hyperthyroidism, as demonstrated by the data of several phase II and III clinical trials (2-5,10,11). The pathophysiological mechanism of thyroid disorder is similar to that of destructive thyroiditis. Thyroid destruction appears to be independent of thyroid autoantibodies and may involve T-cell-, natural killer cell- and/or monocyte-mediated pathways. Activated monocytes infiltrate the thyroid tissue after recognition of antigens similar to tumor antigens and exert their cytotoxic action, indicating the reason behind the temporary nature of the first phase of thyrotoxicosis before returning to normal, or before a possible evolution towards hypothyroidism (1,13). As with the thyroid function reversal of the patient in the present case report, persistent hypothyroidism occurred after four-week hyperthyroidism. The American Society of Clinical Oncology clinical practice guidelines recommend supportive treatment with levothyroxine after ICPI therapy in symptomatic patients with any degree of TSH elevation or in patients with asymptomatic TSH levels that persist at >10 mIU/l, measured 4 weeks apart (6). For persistent hyperthyroidism of >6 weeks, clinical suspicion or work-up for Grave's disease, guidelines recommend treatment with thionamide. In the patient of the present case report, FT4 and TSH levels were monitored every 2 weeks during the transient four-week hyperthyroid phase. Hormone supplementation and monitoring of thyroid function are ongoing since the diagnosis of hypothyroidism. It remains to be determined whether hypothyroidism is permanent and whether the patient will require lifelong support with levothyroxine.

In conclusion, as a promising treatment strategy, immunochemotherapy has demonstrated a meaningful improvement in pCR and survival of patients with triple-negative breast cancer. The present case report provides a new combination regimen of immunotherapy and anthracycline-free chemotherapy for the treatment of early-stage, triple-negative breast cancer, which is worth examining further in a clinical trial. Most immune-related adverse events are reversible and manageable, but hypothyroidism typically requires sustained levothyroxine replacement therapy. How immune-induced thyroid destruction occurs and whether it may be prevented and reversed still needs further exploration.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated and/or analyzed during this study are included in this published article.

Authors' contributions

XZ and FD provided substantial contributions to the design and drafting of the current report. WC interpreted the pathology of the breast and axillary node before and after treatment. CL managed the treatment of the patient in the present report throughout. XZ and FD confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Wuhan Union Hospital (Wuhan, China; approval no. 2023-IEC-302).

Patient consent for publication

The patient provided written informed consent for the publication of any data and/or accompanying images.

Competing interests

The authors declare that they have no competing interests.

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